SUPPORT FOR THE AMENDMENTS

Claims 1-38 and 43-49 were previously canceled.

Claim 39 has been amended.

Claims 57-64 have been added.

The amendment to Claim 39 and the introduction of new Claims 57-64 is supported by original Claims 22-29 and the specification as filed, for example, at pages 16-18 (see, for example, page 17, lines 14-20), page 21, and the Examples.

No new matter has been added by the present amendment.

REMARKS

Claims 39-42 and 50-64 are pending in the present application.

In response to the Notice mailed August 3, 2009, Applicants have amended the claims to be drawn to a method for the treatment of tumors wherein the lethal dose of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide is increased to twice or more, the toxicity at the pharmaceutically effective dosage of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide is reduced, gastrointestinal toxicity at the pharmaceutically effective dosage of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide is reduced, hepatic toxicity at the pharmaceutically effective dosage of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide is reduced, and/or cardiovascular toxicity at the pharmaceutically effective dosage of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide is reduced, which comprises administering to a subject in need thereof a composition comprising

(a) an effective amount of an anti-inflammatory active substance, wherein the anti-inflammatory active substance is a Dexamethasone selected from the group consisting Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone; and

(b) (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide or a salt thereof.

Applicants submit that this amended claim is within the scope of the previously elected invention and, as such, is in proper form for further examination.

The rejection of Claims 39-42 and 50-56 under 35 U.S.C. §103(a) over Nihei et al with Hori et al in view of Fex et al and Sugawara et al are is respectfully traversed.

In the Office Action, the Examiner alleges that the response filed on November 17, 2008, was not persuasive because:

> "Nihei clearly teaches that AC-7700 maintained activity against solid tumors when combined with dexamethasone... it is clear that the end result of the intended use is for the treatment of cancer/tumors. Claim 39 has no limitation as to the population being treated, therefore given the broadest reasonable interpretation, treating cells is well within the purview of the skilled artisan. Nonetheless, Nihei makes it obvious that humans may be treated."

The Examiner further alleges:

> "The results are not commensurate in scope with the claimed invention. The claims recite a combination of drugs, and Applicant's figures show tumors treated with and without dexamethasone with dosages at only 1 point with 1/mg/kg dexamethosone and 10 mg/kg AC-7700. In contrast, the claims recite wide ranges of dexamethasone and AC-7700 as 0.1-10000 mg. In order to show an unexpected result, Applicant should note that there are three major points that should be considered:
>
> > The unexpected results must truly be unexpected,
> >
> > It must be commensurate in scope (show a trend representing the scope, and
> >
> > Lastly, a direct comparison with the closest prior art of record should be provided."

For the reasons already of record, Applicants traverse these allegation by the Examiner. It is correct that Nihei et al contains a disclosure on page 1023, bottom of left column, that "AC-7700 (a) maintained activity against solid tumor growth when combined with dexamethasone". However, as previously argued, this disclosure simply means that activity is maintained but does not provide a reasonable expectation of the present inventors' surprising discovery that the combination of AC-7700 and dexamethasone improves safety

zone of AC-7700 significantly. The Examiner disregards these arguments alleging an expanded safety zone for AC-7700 administration is not claimed

To ensure that the claims are, indeed, commensurate in scope with the demonstrated advantages, Claim 39 has been amended based on page 17, lines 14-20 to be drawn to a method of treating tumors wherein: the lethal dose of AC-7700 is increased to twice or more, the toxicity at the pharmaceutically effective dosage of AC-7700 is reduced, gastrointestinal toxicity (e.g., diarrhea) at the pharmaceutically effective dosage of AC-7700 is reduced, hepatic toxicity (e.g. lowering of GPT) at the pharmaceutically effective dosage of AC-7700 is reduced, and/or cardiovascular toxicity (e.g., lowering of CPK) at the pharmaceutically effective dosage of AC-7700 is reduced, which comprises administering to a subject in need thereof a composition comprising (a) an effective amount of an anti-inflammatory active substance, wherein the anti-inflammatory active substance is a Dexamethasone selected from the group consisting Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone; and (b) (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide or a salt thereof (see Claim 39). Applicants submit that this invention is not obvious over Nihei et al with Hori et al in view of Fex et al and Sugawara et al.

As discussed on pages 1-3 of the specification, tubulin polymerization-inhibitory active substances (e.g., (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide ("AC-7700") have a relatively narrow safety zone between lethal dose and effective dose. Therefore, there are practical and very real limitations on the medicinal use of AC-7700. For the first time, the present Applicants have shown that the safety zone of AC-7700 can be expanded while maintaining anti-tumor effect. To this end, Applicants discovered that the specific combination of the anti-inflammatory active substance "Dexamethasone" reduced the toxicity of AC-7700. Applicants submit that the expansion of

the safety zone of AC-7700 is directly germane to the claimed effects appearing in Claim 39, which are neither disclosed nor suggested by the cited combination of references.

Again, Applicants remind that as set forth in MPEP §716.02(a) "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

In the present case, Applicants have demonstrated in Figures 1 and 2 (see section (6)(1) on page 24) the reduction of AC-7700 toxicity with Dexamethasone. For the Examiner's convenience, Figures 1 and 2 are reproduced below:

Fig.1

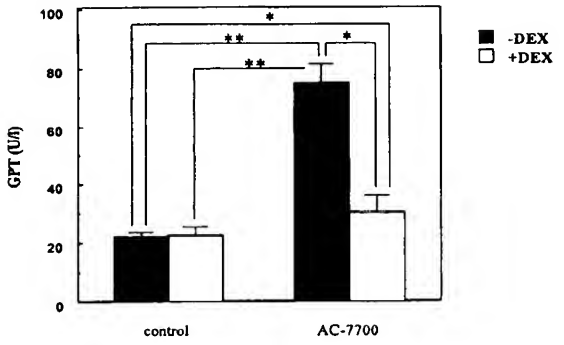

Fig.2

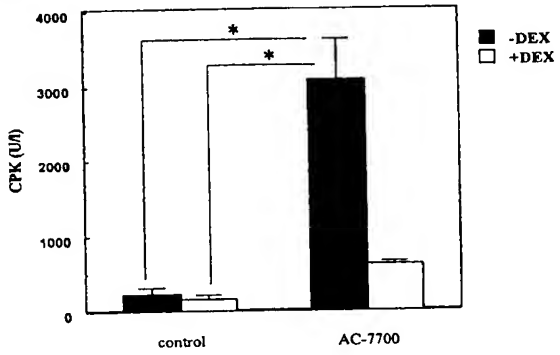

Figure 1 shows results from the toxicity test with tumor-bearing rats from Example 1 (Scheffe's F test; *p<0.05, **p<0.01) F344 rats subcutaneously transplanted MT-9 tumor / Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: GPT; ■: - DEX; □: + DEX. Figure 2 shows results from the toxicity test with tumor-bearing rats in Example 1 (Scheffe's F test; *p<0.05). F344 rats subcutaneously transplanted MT-9 tumor /

Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: CPK; ■ : - DEX; □ : + DEX.

The results reveal that Dexamethasone had remarkably reduced the toxicity of AC-7700 (10mg/kg), hepatic toxicity (GPT) and cardiovascular toxicity (CPK) in tumor bearing rats. Concerning the gastrointestinal toxicity, the combined use of Dexamethasone with AC-7700 has revealed that diarrhea induced by AC-7700 in mice was significantly improved. The toxicity was unexpectedly and significantly improved.

However, if the combination significantly reduces the pharmaceutical effect on anti-tumor simultaneously (reduction of toxicity), it is meaningless and worthless because the safety zone of AC-7700 is not expanded. Applicants discovered that even if both the AC-7700 and Dexamethasone were administered, there was no significant deference in the pharmaceutical effect between AC-7700 alone and combination of AC-7700 and Dexamethasone as shown in Table 1 (below).

[Table 1] Influence of Dexamethasone on the pharmaceutical effect of AC-7700

DEX(mg/kg/day)	AC-7700(mg/kg/day)	I.R.(%)
0	0	0
0	10	84**
1	0	21
1	10	72**

(Note: Mann-Whitney's U test; **: $p<0.01$ vs. Control)

Nihei et al disclose that "AC-7700 (a) maintained activity against solid tumor growth when combined with Dexamethasone", but this means activity is maintained. The present inventors surprising found that the combination of AC-7700 and Dexamethasone improves safety zone of AC-7700 significantly, so at least such a combination is very worthy and valuable in practical use of AC-7700. Such effects of the combination are not disclosed and not suggested in the prior arts and advantageous effects are unpredictable.

Applicants submit that at the time that this application was filed, it was unknown that a combination tublin polymerization inhibitory active agent (AC-7700) and anti-inflammatory active substance (Dexamethasone) expands the narrow safety zone of tublin polymerization inhibitory active agent. Thus, Applicants submit that the present invention would not be obvious.

Although acknowledging that the foregoing results are unexpected, the Examiner largely disregards the evidence in Figures 1 and 2 for the claimed invention alleging that the results are not commensurate in scope. Applicants submit that the foregoing results are relevant to and commensurate in scope with the presently claimed method: increasing the lethal dose of AC-7700 to twice or more, reducing the toxicity at the pharmaceutically effective dosage of AC-7700, reducing gastrointestinal toxicity (e.g., diarrhea) at the pharmaceutically effective dosage of AC-7700, reducing hepatic toxicity (e.g. lowering of GPT) at the pharmaceutically effective dosage of AC-7700, and/or reducing cardiovascular toxicity (e.g., lowering of CPK) at the pharmaceutically effective dosage of AC-7700. Further, Applicants submit that these results are representative of the claimed invention as each of the claimed forms of Dexamethasone (Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone) still contain the dexamethasone structure and, therefore, would

be expected to demonstrate the same effect. As such, Applicants submit that the results above would rebut even a *prima facie* case of obviousness.

Withdrawal of these grounds of rejection is requested.

Applicants submit that the present application is now in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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